

Impact of adrenal steroid receptors for myocardial healing and remodeling



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Activation of the mineralocorticoid receptor (MR) in different cells of the heart plays a major role in the pathophysiology of myocardial healing and remodeling as well as heart failure progression. MR expression is increased in preclinical models of cardiovascular disease, and MR activation critically contributes to ventricular hypertrophy, ischemia/infarction and myocardial injury. Increased aldosterone levels are not a prerequisite of MR activation in the cardiovascular system, instead MR dependent signaling may also be activated by cortisol and/or oxidative stress.

Cell-specific ablation of the MR in cardiomyocytes led to attenuation of myocardial hypertrophy, fibrosis, and oxidative stress as well as reduced heart failure progression in mice after myocardial infarction. Cell-specific ablation of the MR in monocytes/macrophages improved myocardial remodeling, while ablation of the glucocorticoid receptor (GR) in monocytes/macrophages lead to adverse healing and enhanced left ventricular dilatation and rupture after myocardial infarction.

In patients with cardiovascular disease, MR antagonists prevent or attenuate increases in markers of oxidative stress, inflammation, fibrosis and tissue injury in the heart. MR antagonists significantly reduce mortality and morbidity in patients with chronic heart failure, or heart failure after acute myocardial infarction.

Recent phase 2 studies in patients with heart failure and kidney dysfunction using novel non-steroidal MR antagonists indicate that these compounds may have a more favourable risk-benefit profile with maintained or even enhanced cardiovascular risk reduction and less risk of hyperkalemia and worsening renal function. However, these results have to be confirmed in adequately powered phase 3 trials.

Selected publications

- *Mineralocorticoid Receptor Activation and Mineralocorticoid Receptor Antagonist Treatment in Cardiac and Renal Diseases.* Bauersachs J, Jaisser F, Toto R. Hypertension. 2015;65:257-263.
- *Efficacy of mineralocorticoid receptor antagonism in the acute myocardial infarction phase: eplerenone versus spironolactone.* Fraccarollo D, Galuppo P, Sieweke JT, Napp LC, Grobecker P, Bauersachs J. ESC Heart Fail; 2015
- *Mineralocorticoid receptor antagonists for therapy of coronary artery disease and related complications.* Zwadlo C, Bauersachs J. Curr Op Pharmacol 2013, 13:280-286
- *The ARTS of third-generation mineralocorticoid receptor antagonists: achieving cardiovascular benefit with minimized renal side effects?* Bauersachs J. Eur Heart J. 2015 doi:10.1093/eurheartj/eh235
- *Novel therapeutic approaches to post-infarction remodeling.* Fraccarollo D, Galuppo P, Bauersachs J. Cardiovasc Res. 2012, doi:10.1093/cvr/cvs109
- *Deletion of cardiomyocyte mineralocorticoid receptor ameliorates adverse remodeling after myocardial infarction.* Fraccarollo D, Berger S, Galuppo P, Kneitz S, Hein L, Schutz G, Frantz S, Ertl G, Bauersachs J. Circulation 2011;123:400-408.
- *Impairment of endothelial progenitor cell function and vascularization capacity by aldosterone in mice and humans.* Thum T, Schmitter K, Fleissner F, Wiebking V, Dietrich B, Widder JD, Jazbutyte V, Hahner S, Ertl G, Bauersachs J. Eur Heart J 2011;32:1275-1286.
- *Immediate Mineralocorticoid Receptor Blockade Improves Myocardial Infarct Healing by Modulation of the Inflammatory Response.* Fraccarollo D, Galuppo P, Schraut S, van Rooijen N, Ertl G, Bauersachs J. Hypertension 2008;51:905-914
- *Additive improvement of left ventricular remodeling and neurohormonal activation by aldosterone receptor blockade with eplerenone and ACE inhibition in rats with myocardial infarction.* Fraccarollo D, Galuppo P, Hildemann S, Christ M, Ertl G, Bauersachs J. J Am Coll Cardiol 2003; 42:1666-1673

Curriculum Vitae

Career:

- 13.12.1993 Thesis (M.D.) at the University of Freiburg, Department of Physiology
1993-1995 Residency and Fellowship in Internal Medicine, University Hospital Frankfurt
1995-1996 Postdoctoral/Research Associate, Physiology, University of Frankfurt
1996-1999 Residency and Fellowship in Internal Medicine, University Hospital Mannheim
1999-2003 Residency and Fellowship in Internal Medicine and Cardiology, Department of Medicine, University of Würzburg
1999-2004 Scientific Secretary DFG Special Research Program SFB 355
2000 Board Certification „Internal Medicine“
2002 Board Certification „Cardiology“
2001 Habilitation, Member of the Faculty, senior lecturer, Dept. of Medicine, Division of Cardiology, University of Würzburg
2003-2010 Consultant Cardiology/Intensive Care, University Hospital Würzburg
2006-2010 Scientific Secretary DFG Special Research Program SFB 688
2008 Board Certification „Intensive Care“
2008-2010 Associate Professor, Dept. of Medicine I, Division of Cardiology, University Hospital Würzburg
01/2010 Call for W3-Professorship Cardiology/Angiology, University Hospital Giessen
since 10/2010 Full Professor and Director, Department of Cardiology and Angiology, Hannover Medical School

Special achievements/honors:

- 2001 Oskar-Lapp- Award, „Deutsche Gesellschaft für Kardiologie“
2004 Albert-Fraenkel-Award, „Deutsche Gesellschaft für Kardiologie“
2006 Parmley-Award, American College of Cardiology
2012 Bernard and Joan Marshall Distinguished Investigator Award, British Society for Cardiovascular Research

President of:

ESAC Germany (European Section of Aldosterone Council) Association

Member of:

- Deutsche Forschungsgemeinschaft (DFG) - Fachkollegium Medizin
- Deutsche Gesellschaft für Kardiologie - Herz- und Kreislaufforschung - Member Program Committee
- Deutsche Gesellschaft für Innere Medizin
- Fellow American Heart Association
 - Council on Basic Cardiovascular Sciences
 - Council on Clinical Cardiology
- Fellow European Society of Cardiology
 - Heart Failure Association (HFA), Fellow, Board Member
 - Chair HFA Study Group Peripartum Cardiomyopathy
 - Past Chair, Working Group on Myocardial Function

Editorial Board Member:

Hypertension, Cardiovascular Research, Clinical Research in Cardiology, Basic Research in Cardiology, European Journal Clinical Investigation

Reviewer for:

Deutsche Forschungsgemeinschaft, Deutsche Herzstiftung, Circulation, Circulation Research, Hypertension, Arteriosclerosis, Thrombosis and Vascular Biology, Journal of the American College of Cardiology, European Heart Journal, Cardiovascular Research, European Journal of Heart Failure, Journal of Molecular and Cellular Cardiology, British Journal of Pharmacology, European Journal of Clinical Investigation, Thrombosis Haemostasis, Endocrinology, American Journal of Physiology, Atherosclerosis, Diabetes, etc

Research interests:

Professor Bauersachs is an interventional cardiologist with special interests in acute coronary syndromes, left ventricular healing and remodelling, acute and chronic heart failure, as well as intensive care. He is particularly interested in aldosterone and mineralocorticoid receptor-mediated mechanisms and the role of non-coding RNAs.

Main research areas of the Department:

- Regeneration and adaptation in the cardiovascular system
- Peripartum cardiomyopathy
- Molecular and cellular mechanisms of heart failure development and progression
- Implantable cardioverter defibrillator with heart failure early warning systems
- Vascular remodeling and regeneration

Important recent publications:

- *Peripartum cardiomyopathy: current management and future perspectives.* Hilfiker-Kleiner D, Haghikia A, Nonhoff J, **Bauersachs J** (2015). Eur Heart J, DOI: <http://dx.doi.org/10.1093/eurheartj/ehv009>, first published online: 30 January 2015
- *Anti-androgenic therapy with finasteride attenuates cardiac hypertrophy and left ventricular dysfunction.* Zwadlo C, Schmidtmann E, Szaroszyk M, Kattih B, Froese N, Hinz H, Schmitto JD, Widder J, Batkai S, Bähre H, Kaever V, Thum T, **Bauersachs J**, Heineke J (2015). Circulation, 131:1071-1081.
- *Mineralocorticoid receptor activation and mineralocorticoid receptor antagonist treatment in cardiac and renal diseases.* **Bauersachs J**, Jaisser F, Toto R (2015). Hypertension 65, 257-263.
- *Cardiac angiogenic imbalance leads to peripartum cardiomyopathy.* Patten IS, Rana S, Shahul S, Rowe GC, Jang C, Liu L, Hacker MR, Rhee JS, Mitchell J, Mahmood F, Hess P, Farrell C, Koulisis N, Khankin EV, Burke SD, Tudorache I, **Bauersachs J**, del Monte F, Hilfiker-Kleiner D, Karumanchi SA, Arany Z (2012). Nature 485, 333-338.
- *Novel therapeutic approaches to post-infarction remodelling.* Fraccarollo D, Galuppo P, **Bauersachs J**. (2012). Cardiovasc Res 94, 293-303.
- *Deletion of cardiomyocyte mineralocorticoid receptor ameliorates adverse remodeling after myocardial infarction.* Fraccarollo, D., Berger, S., Galuppo, P., Kneitz, S., Hein, L., Schütz, G., Frantz, S., Ertl, G., **Bauersachs, J.** (2011). Circulation 123, 400-408.
- *Biogenesis and regulation of cardiovascular microRNAs.* **Bauersachs J**, Thum T. (2011). Circ Res 109, 334-47.

- *Impairment of endothelial progenitor cell function and vascularization capacity by aldosterone in mice and humans.* Thum T, Schmitter K, Fleissner F, Wiebking V, Dietrich B, Widder JD, Jazbutyte V, Hahner S, Ertl G, **Bauersachs J.** (2011). *Eur Heart J* 32, 1275-86.
- *MicroRNA-21 contributes to myocardial disease by stimulating MAP kinase signalling in fibroblasts.* Thum, T., Gross, C., Fischer, T., Fiedler, J., Just, S., Rottbauer, W., Bussen, M., Galuppo, P., Frantz, S., Castoldi, M., Muckenthaler, M., Soutschek, J., Koteliansky, V., Rosenwald, A., **Bauersachs, J.***, Engelhardt, S.* (2008). *Nature* 456, 980-984. *joint senior authors
- *Immediate mineralocorticoid receptor blockade after myocardial infarction improves infarct healing by modulation of the inflammatory response.* Fraccarollo D, Galuppo P, Schraut S, Kneitz S, van Rooijen N, Ertl G, **Bauersachs J.** (2008). *Hypertension* 51, 1-10.
- *Improvement of left ventricular remodelling by the endothelial nitric oxide synthase enhancer AVE9488 after experimental myocardial infarction.* Fraccarollo D, Widder JD, Galuppo P, Thum T, Hoffmann M, Ruetten H, Ertl G, **Bauersachs J.** (2008). *Circulation* 118, 818-82.
- *MicroRNAs in the human heart: A clue to fetal gene reprogramming in heart failure.* Thum T, Galuppo P, Wolf C, Fiedler J, Kneitz S, van Laake LW, Doevendans PA, Mummery CL, Borlak J, Haverich A, Gross C, Engelhardt S, Ertl G, **Bauersachs J.** (2007). *Circulation* 116, 258-267.